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MINISTRY OF AGRICULTURE, FISHERIES AND FOOD

MEMORANDUM ON PROCEDURE FOR SUBMISSIONS ON FOOD ADDITIVES AND ON METHODS OF TOXICITY TESTING

[illegible] 1965

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INTRODUCTION

1. This memorandum is intended as a guide to commercial and other organisations concerned with the use of additives in food about (1) administrative procedures followed by Government Departments, the Food Additives and Contaminants Committee and its Pharmacology Sub-Committee and (2) toxicity testing.

PART I

Government Departments and Committees

2. The Government Departments in the United Kingdom concerned with the control of food additives are the Ministry of Agriculture, Fisheries and Food and the Ministry of Health (the former taking primary administrative responsibility in England and Wales), the Scottish Home and Health Department, and the Ministry of Health and Social Services for Northern Ireland. The responsible Ministers receive independent advice from the Food Additives and Contaminants Committee on matters referred to it by Ministers, in relation to food contaminants, additives and similar substances which are or may be present in food, or used in its preparation, with particular reference to the exercise of powers conferred on Ministers by Sections 4, 5 and 7 of the Food and Drugs Act, 1955 and the corresponding provisions in enactments relating to Scotland and Northern Ireland. The Committee's Pharmacology Sub-Committee advises on hazards to health and may seek advice from other specialist bodies, including the Chief Medical Officer of the Ministry of Health's Committee on Medical and Nutritional Aspects of Food Policy.

3. The Food Standards Division of the Ministry of Agriculture, Fisheries and Food provides the administrative and technical secretariat to the Food Additives and Contaminants Committee and the Pharmacology Sub-Committee. All communications concerned with matters in the field of work covered by this memorandum whether intended for consideration by Government Departments, or for reference to the Committee and Sub-Committee, should be addressed to the Food Standards Division, Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, London, S.W.1.

Procedure for General Reviews of Regulations on Classes of Additives

4. It is hoped to make quinquennial reviews of each of the regulations on food additives. Prior to a general review of existing regulations, or the initial consideration of a fresh group of additives, an announcement is made by the responsible Ministers through the Press inviting comment or proposals. Representations received will be considered as quickly as possible by the Food Additives and Contaminants Committee and the Pharmacology Sub-Committee according to the terms of reference. It is open to an organisation to seek an interview with the Food Additives and Contaminants Committee or the Pharmacology Sub-Committee and for either of these bodies to ask for a discussion with the organisation which has made representations. Reports to Ministers by the Committee will usually be published, but do not necessarily commit Ministers to acceptance of the Committee's recommendations. Comments on published reports are invited through the Press by Ministers and are taken into account before action is taken. Consultations take place on as wide a basis as is necessary and proposals for legislation are published for comment before final decisions are taken on the making of regulations.

Procedure for Individual Applications for Amendment to Regulations

5. A particular food additive may be proposed for consideration at any time. In such a case the foregoing procedure outlined in paragraphs 3 and 4 will apply

in principle. Departments will require to consider whether on grounds of need the time is appropriate for a submission to be made to the Food Additives and Contaminants Committee. When it is proposed to postpone the submission until the next review, it will of course be open to an organisation to make further representations.

General

6. Government Departments and the Food Additives and Contaminants Committee have regard to the reduction as far as possible of the use of non-nutritive substances in food, (Section 4(2) of the Food and Drugs Act, 1955), to the desirability of keeping to a minimum the number of permitted additives consistent with reasonable trade requirements and to the overriding considerations *of public health.* It is desirable therefore that any application for a proposed new additive should show the need for it and that the same objectives could not be obtained by good manufacturing practices or by existing approved additives. The Committee may question the proposal on this score, and if they do the firm will be informed. It will, of course, be open to the firm to argue the issue.

7. The Food Additives and Contaminants Committee, and the Pharmacology Sub-Committee make recommendations to Ministers on the available evidence whether or not a particular additive taken in food is likely to be harmful to man. The kind of evidence and some of the principles to be followed on laboratory testing are given below. It is hoped that this guidance will obviate expenditure of time and money on trials unlikely to produce adequate evidence for assessment of hazard to health. An opportunity will be provided for either the organisation or the appropriate committee or Sub-Committee to ask for a discussion on any proposed tests. During the actual tests themselves, information may come to light which would permit the shortening or require the extension of the amount of test required. The Pharmacology Sub-Committee will in these circumstances be ready to advise on any change in programme which may be proposed. Every effort will be made to assist firms to conduct trials and submit their results in the best manner.

8. There may be occasions when a substance is submitted for consideration on the basis of published information, or unpublished work already done, so that no question arises of the Committee being consulted about the scheme of testing. The procedure already described will operate, as applicable, to submissions of this kind and the Committee may, when the evidence is presented to them, express the opinion that it is inadequate and ask for tests, or further tests, to be carried out. In this event the firm will be able to seek the advice of the Committee in the way already described. No undertaking can be given in advance that the results of any proposed trials will be accepted as conclusive; nor can it be specified in advance what results will satisfy the Committee in a particular series of tests.

9. Communications from commercial and other organisations will be treated as confidential documents by Departments and the Committee. The Food Additives and Contaminants Committee's Reports may disclose that an application was made for a stated substance, but will not disclose the name of the applicant. If the Committee recommends that a substance should be permitted, its Report may quote or refer to the scientific work on which its conclusions are based, whether or not that work has been published. If the recommendation is that a substance should not be permitted, unpublished work submitted in support of it will not be quoted or referred to in the Report. In this case, if the Department receives a request from any source for information about the grounds on which

the unfavourable recommendation was made, it will not make any disclosure without first obtaining the agreement of the firm or organisation which submitted the substance.

PART II

Testing of Food Additives

10. It would be impossible to arrive at a complete assurance of the safety of a substance unless it had been ingested in food by persons of all ages in specified amounts over long periods and been shown conclusively, by a careful medical follow-up, to have had no harmful results. A substance might also be considered safe as a result of an accurate knowledge of its metabolism. In practice few compounds at present fall into either of these categories, but where they are considered to do so, submissions may be made on that basis.

11. Usually a comprehensive series of laboratory tests with animals is necessary. Extrapolation to man from toxicity tests in animals has obvious limitations but for the time being, such tests are the main basis for toxicological prediction. The following paragraphs are concerned with the principles of testing, not the techniques. The techniques have already been set out in the SECOND and FIFTH Reports of the joint FAO/WHO Expert Committee on Food Additives[1,2], which are available at H.M.S.O., and which should be followed except where this memorandum requires otherwise.

12. It may be thought that the suggested requirements are unnecessarily extensive. It must be borne in mind that most additives by their very nature are of low toxicity and the possible hazards to man are therefore difficult to define, even after the completion in the laboratory of an investigation that seems to be both comprehensive and exhaustive. The conclusions reached about the likely hazards to man can be no more than tentative, and they may have to be reviewed later in the light of further evidence, and particularly that which comes to hand in practice and from experience with man.

13. Details will be required on the following:

(i) *Composition, purity* and *commercial usage*;

(ii) *Acute toxicity*, both oral and parenteral, for rats and mice, and at least one other animal species preferably non-rodent;

(iii) *Short-term studies*, from feeding tests at several dietary levels, on rats or mice, together with at least one other animal species preferably non-rodent; in the case of rats and mice this should amount to 90 days and in the case of other animals to 10% of their normal span of life.

(iv) *Long-term studies including Carcinogenicity*, from tests following the guide issued by the Ministry of Health's Panel on Carcinogenic Risks in Food Additives and Contaminants[5]. These tests should also be used to detect any long-term toxicity not apparent in the short-term studies; and should extend over the whole of the animal's life. It is also desirable to submit evidence of effects on fertility.

(v) *The metabolism*, including, where appropriate, its effect on enzyme activity;

(vi) *The effect on man*, whenever evidence can be obtained from existing sources.

Composition

14. Not all food additives are chemically pure compounds with well-defined properties as some are mixtures of related chemicals and most contain impurities.

15. For every substance used, or intended for use, as a food additive the first task therefore must be to provide an adequate specification to show its composition, standard of purity and the nature and quantity of contaminants. This should be supplemented by methods of analysis by which these characteristics can be determined. In some instances this can be met by reference to published standards, for example, in the British Pharmacopoeia or the specifications for preservatives, antioxidants and colours in the Third and Fourth Reports of the joint FAO/WHO Expert Committee on Food Additives[3,4].

16. The material on which the toxicity tests are undertaken should be the same as that produced or proposed to be produced commercially for use in food and should conform to the same specification.

Toxicity Tests

17. In designing toxicity tests the commercial usage of a particular additive must be borne in mind. For example, if the foodstuff treated with the additive is to be cooked before eating, that component of the test diet should be similarly heated beforehand. The difficulties to be met are due to the differences between human and animal diets and emphasise the need of prior consultation on testing to prevent needless tests being made and essential ones being neglected.

18. The evaluation of evidence of the action of chemical compounds on animals is only possible when the data have been collected by a competent worker and include all relevant details of the experiments.

19. Toxicity tests themselves should include a study of the largest single dose an animal will tolerate, the largest daily dose it will accept for a limited period of at least three weeks, and the effects of a daily dose given to animals for 90 days or longer which *pro rata* is an appropriate multiple of the estimated maximal human intake.

Acute Toxicity

20. These tests should be made on rats and mice of both sexes and on one other species, which should preferably be a non-rodent, by both oral and parenteral routes so that it is possible to estimate within reasonable limits the largest non-fatal and the smallest fatal dose. A single dose toxicity by oral and parenteral routes with an appropriate LD 50 should be estimated. Administration to a group of even two animals of several species may exclude gross differences in sensitivity in those species. It is even more important, however, to record the time course and characteristics of the poisoning with full details of behavioural changes and the pathological findings. Studies of acute toxicity should be continued until it is possible to give some opinion on the apparent mode and site of action of the substance. Finally in these acute tests attention should be paid to any changes in toxicity that may arise from storage or from admixture with foodstuffs.

Short-Term Studies

21. Short-term studies should be conducted with at least two species of animals of both sexes, one of which should not be a rat or mouse and should preferably

be a non-rodent. The additive should be administered daily in the diet. Guidance on numbers of animals should be obtained from the Second and Fifth Reports of the joint FAO/WHO Expert Committee on Food Additives.

22. Dose concentrations are important. From evidence obtained during the calculation of the LD 50, an estimate should be made of the highest dose which will permit the survival of the animals for at least 3 weeks. Of the other concentrations tested, the choice of the lowest amount in the diet of the animal should be based on the intended intake of the additive in food as consumed. An approach to the problem is to assume in most instances that the food so treated may furnish as much as one half of the daily calorie requirements of man for the greater part of his life. Special care may need to be exercised over the proportion of a non-nutritive substance in the test diet.

23. With the lower doses, observation should be continued for at least ninety days or 10% of the normal life span and a comparison made between the general condition and rate of growth of treated and control animals. All of the animals, including those surviving to the end of the experiment, should be examined post-mortem and the report should include details of any macroscopic or microscopic changes in the organs. When the nature of the chemical indicates that it is likely to have effects on enzyme systems, these latter should be studied.

Long-Term Studies Including Carcinogenicity

24. The guide issued by the Panel on Carcinogenic Risks in Food Additives and Pesticides[5] should be followed as far as possible. The programme should only be modified in this respect after reference in the first place to Food Standards Division of the Ministry of Agriculture, Fisheries and Food.

25. Such tests over the greater part of the animals' life span give the opportunity to detect any long-term toxicity not previously revealed in the short-term studies. Some of this evidence may be difficult to interpret because of the effects of aging in the animals and for this reason cannot totally supplant the ninety day test. It is also desirable to submit evidence of effects on fertility.

Metabolic Studies

26. It has already been stated that knowledge about the metabolic fate of any food additive in man is an important way of determining whether it is likely to be completely safe. Any information therefore about absorption, distribution, tissue storage, and ultimate fate of any substance in animals is of great importance in reaching a conclusion about toxicity. If a substance has no toxic actions, the fate of the dose administered might be traced so that its harmlessness might be explained—failure of absorption, rapid and complete excretion or conversion to a physiological metabolite. Because such evidence may be difficult to obtain through lack of facilities, it is not suggested that such information must be included in all submissions. Nevertheless it should be the aim of the industry to provide information of this kind, and the Pharmacology Sub-Committee will attach great importance to it when it can be provided.

Assessment of Toxicity Data

27. There is no general agreement about the extrapolation of results from animal experiments to man. For example, man consumes 1/100th of his body weight as food daily and the mouse 1/10th. The composition of the human diet is very different from that which will keep rodents healthy and there may be a

relationship between the effect of a food additive and the proportion of carbohydrate, fat, or protein in the diet. There are certain conditions occurring in man that are extremely difficult to reproduce in animals, for example, agranulocytosis, anaphylactoid purpura and allergic conditions, and subjective symptoms of importance in man cannot be detected in animals. In relating the maximum daily tolerated dose producing no ill effects in animals with the daily intake for man, a safety factor of 100 is commonly employed. This factor should not, however, be regarded as an invariable guarantee of safety and it may have to be considerably increased in particular cases. In other cases the use of a factor as high as 100 may result in the test animal receiving a diet of which the non-nutritive additive comprises the major part. Because of these limitations on the value of animal experiments, efforts should always be made to obtain evidence of the effect of food additives on man. Sometimes evidence from pharmacological sources exists, and, in other cases, there may be evidence about closely related substances. Submissions should, therefore, always give some account of what steps have been taken to obtain evidence in relation to man.

Reference
FS 1938 *January 1965*

References

[1] Procedures for the Testing of International Food Additives to Establish their Safety for Use; Second Report of the Joint FAO/WHO Expert Committee on Food Additives: FAO/WHO, Rome 1958.

[2] Evaluation of the Carcinogenic Hazards of Food Additives: Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives: FAO/WHO, Rome 1961.

[3] Specifications for Identity & Purity of Food Additives (Antimicrobial Preservatives and Antioxidants): Third Report of the Joint FAO/WHO Expert Committee on Food Additives: FAO/WHO, Rome 1959.

[4] Specifications for Identity & Purity of Food Additives (Food Colours): Fourth Report of the Joint FAO/WHO Expert Committee on Food Additives: FAO/WHO, Rome 1960.

[5] Monthly Bulletin of the Ministry of Health 1960, 19. 108

Publications Nos. (1)—(4) are available from Her Majesty's Stationery Office. Publication No. 5 is available from Ministry of Health, Division H.S. 2 B(h) Alexander Fleming House, Elephant and Castle, S.E.1.

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